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EXAMINER

18M1/1126
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GAMBEL P	PAPER NUMBER
ART UNIT	

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17

DATE MAILED: 11/26/97

This is a communication from the examiner in charge of your application.
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OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 8/4/97

☐ This action is FINAL.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

- ☒ Claim(s) 1-25 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
- ☐ Claim(s) _____ is/are allowed.
- ☒ Claim(s) 1-25 is/are rejected.
- ☐ Claim(s) _____ is/are objected to.
- ☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

- ☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- ☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
- ☐ The specification is objected to by the Examiner.
- ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- ☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been
- ☐ received.
- ☐ received in Application No. (Series Code/Serial Number) _____
- ☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

- ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- ☒ Notice of Reference Cited, PTO-892
- ☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
- ☒ Interview Summary, PTO-413 AND ADVISORY ACTION ⇒ ALREADY OF RECORD
- ☐ Notice of Draftsperson's Patent Drawing Review, PTO-948
- ☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

DETAILED ACTION

1. Since this application is eligible for the transitional procedure of 37 CFR 1.129(a), and the fee set forth in 37 CFR 1.17(r) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.129(a). Applicant's first submission after final filed on 8/4/97 (Paper No. 14) has been entered. Also, upon request, applicant's after final amendment, filed 6/9/97 (Paper No. 10) has been entered.

Claims 1 and 24 have been amended.

Claims 1-25 are pending and being acted upon presently.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Office Action.

This Action will be in response to applicant's arguments, filed 6/9/97 (Paper No. 10) and filed 8/4/97 (Paper No. 14).

The rejections of record can be found in the previous Office Actions (Paper Nos. 7, 9 and 12).

3. Formal drawings and photographs have been submitted which fail to comply with 37 CFR 1.84. Please see the enclosed form PTO-948.

Applicant is reminded to change the Brief Description of the Drawings in accordance with these changes (see 7. Views).

4. In view of applicant's amendment, filed 8/4/97 (Paper No. 14), for amending claims 1 and 24, filed 6/9/97 (Paper No. 10) (versus the previous citation for support in the specification); the previous new matter issues raised in the Advisory Action (Paper No. 12), have been obviated.

The priority date of the claimed limitations drawn to ratio such that 25 to 75% saturation of IL-2 receptors is that of the instant application, that is, 6/7/95.

5. Applicant's arguments, filed 6/9/97 (Paper No. 10) and filed 8/4/97 (Paper No. 14), have been fully considered but are not found convincing for the reasons of record.

Applicant's argues that the instant invention arises from the difficulties in the art in providing a balance between antibody and cytotoxic agent and that the instant invention has identified that optimal dosing is produced by saturating 25-75% of the IL-2 receptors and that this dosage range is determined by the patient's IL-2R level.

Applicant's arguments addressing the prior art teachings of therapeutic modalities such as murine antibodies, humanized antibodies and antibody-toxin conjugates do not obviate the clear teachings of the these same prior art references employing the same antibody-radionuclide including ⁹⁰Y, dosages and patient populations including therapeutic efficacy in clinical trials as applicant's instant disclosure and claimed invention.

Also, applicant's reliance on Waldmann (Science, 1991; Exhibit 1 in Paper No. 10) to indicate that the use of murine antibodies was disappointing clinical and that this would have discouraged pursuit for a method of anti-Tac treatment is not found convincing. Clearly, the prior art references of record successfully employed anti-Tac antibodies therapeutically in human patients. Also, it was known at the time the invention was made that recombinant antibodies were made to obviate or lessen the immunogenicity limitations in the use of murine antibodies as diagnostic or therapeutic agents in humans.

A) The claimed limitations incorporating the limitation drawn to a therapeutic amount "provided in a ratio of anti-Tac to ^{90}Y , said ratio comprising" 2-100 mg of anti-Tac to 5-15 mCi ^{90}Y conjugate, "said ratio based upon soluble IL-2 receptor levels, such that 25 to 75% saturation of total IL-2 receptors is provided" (recited in claim 1) or "wherein the effective dose is provided in a ratio of anti-Tac to cytotoxin-conjugate, said ratio sufficient to produce 25 to 75% saturation of IL-2 receptors by said cytotoxin-conjugate" (recited in claim 24) are acknowledged. However, these claim limitations merely recite properties associated with the same dosages of anti-Tac conjugate disclosed and taught by the prior art. Again, applicant has not distinguished the instant dosages from that of the prior art. Further the prior art is applicant's own work and applicant has not provided any objective evidence to indicate that by using the same antibody conjugates and dosages employed in these references differ from that encompassed by the instant claims.

Therefore, applicant's arguments have not been found persuasive in that the "ratio of anti-Tac to ^{90}Y " limitations argued by applicant are met either as being anticipated or as being obvious over the use of the same dosages taught in the prior art and encompassed by the claims. Also, the claimed range of 25-75% saturation of IL-2 receptors is a broad range which would have been met by the administration of therapeutic anti-Tac conjugates taught by the prior art. These "ratio of anti-Tac to ^{90}Y " limitations argued by applicant do not add additional limitations (e.g. method steps) over the dosage or amount of "2-100 mg of anti-Tac to 5-15 mg mCi ^{90}Y " or "a cytotoxin-conjugated anti-Tac antibody wherein the cytotoxin is either ^{90}Y or ricin A" encompassed by the previous and instant claims. Also note that claims 19-23 are drawn to "10-100 ug/kg anti-Tac doses" and do not recite "ratio of anti-Tac to ^{90}Y ".

B) Alternatively, if applicant intends to amend the claims to recite distinct method steps drawn to determining the "ratio of anti-Tac to ^{90}Y " as specific limitations, the following is noted.

It is noted that applicant argues that the determination of total IL-2R and the percent saturation was well known in the art (e.g. Rubin et al. Ann. Intern. Med., 1990) and set forth in the instant specification and that soluble IL-2R is directly proportional to total IL-2R levels in a patient (see page 3 of Paper No. 14).

Also, the written support on page 52 on the instant specification for amending the claims to incorporate limitations drawn to "ratios" discloses that: "the dose of humanized anti-Tac administered may be adjusted on the basis of the estimate of the serum soluble IL-2R level obtained within 3 weeks prior to the dose administration. The levels of anti-Tac are those estimated yield binding of tumor cells and to produce approximately 25 to 75% saturation of the IL-2 receptors. These calculations are made on the basis of the observation during the Phase I trial, where the binding was assessed by FACS analysis and by binding to the circulating cells of ^{111}In -anti-Tac to coadministered with ^{90}Y -anti-Tac."

In addition, page 13, paragraph 5 and Example 17 of the instant specification that bioavailability studies during the Phase I trials using anti-Tac, an algorithm to predict a dose of total anti-Tac (sum in mg of unlabeled and labeled antibody) that was sufficient to overcome the effect of soluble antigen levels (i.e. sIL-2R) without excessively diluting antibody specific activity".

Therefore, it appears from applicant's own admission and disclosure that the determination of total IL-2R in patient populations was known and used at the time the invention was made and that bioavailability studies including algorithms to overcome the effect of soluble IL-2R without diluting antibody specific activity were developed and employed during Phase I trials with anti-Tac antibody-radionuclide conjugates.

Again, it is pointed out that the prior art relies upon applicant's own work employing the same anti-Tac antibody-radionuclide conjugates in the same or nearly the same Phase I and Phase II clinical trials. Although the parameters of the clinical trials are not in the PTO's possession; it is prima facie obvious that the clinical trials of the prior art were performed with same parameters of monitoring the bioavailability of soluble IL-2R as the instant invention, in the absence of objective evidence to the contrary. This is particularly evident considering that the prior art relied upon encompasses various review articles by applicant himself, indicating that this information was known and employed by others at the time the invention was made.

Therefore in view of applicant's possible intent to claim the determination of anti-Tac to radionuclide ratios as a separate limitation of the instant invention, it would have been obvious to determine conduct bioavailability analysis to achieve saturation of IL-2 receptors to overcome the effect of soluble IL-2R without diluting antibody specific activity at the time the invention was made to maintain and to achieve efficacy of anti-Tac antibody-radionuclide conjugates. Therefore, managing the treatment of the various diseases targeted by anti-Tac antibody radionuclide (or cytotoxin) conjugates would have resulted in providing ratios of anti-Tac to ^{90}Y , said ratio comprising "2-100 mg of anti-Tac to 5-15 mCi ^{90}Y conjugate, "said ratio based upon soluble IL-2 receptor levels, such that 25 to 75 % saturation of total IL-2 receptors is provided" (recited in claim 1) or "wherein the effective dose is provided in a ratio of anti-Tac to cytotoxin-conjugate, said ratio sufficient to produce 25 to 75 % saturation of IL-2 receptors by said cytotoxin conjugate" (recited in claim 24)

C) Rebuttal to applicant's arguments concerning the prior art of record.

Applicant argues that Waldmann (Ann. Oncol.) provides no teaching or suggestion regarding the claimed effective dosage, i.e. the ratio of conjugated anti-Tac to non-conjugated anti-Tac. Applicant argues that this reference fails to suggest a specific ratio or conjugated antibody and the degree of saturation required to provide an effective dosage.

However, this Waldmann (Ann. Oncol.) reference authored by applicant clearly teaches the use of same 5-15 mCi ^{90}Y -labeled anti-Tac antibody in Phase I and Phase II trials (page 16, column 1 paragraph 2). The range of 2-100 mg of anti-Tac antibody provided with 5-15 mCi ^{90}Y -labeled anti-Tac antibody recited in the claims is a broad range as well as 25-75 % saturation of total IL-2 receptors and surely would have been encompassed by the use of the same 5-15 mCi ^{90}Y -labeled anti-Tac antibody disclosed in the prior art. Applicant has not provided objective evidence to indicate that the prior art teachings do not meet the effective dosages including the saturation of IL-2 receptors encompassed by the claims.

Applicant argues that Waldmann (Imp. Adv. Oncol.) provides no teaching or suggestion regarding the claimed effective dosage, i.e. the ratio of conjugated anti-Tac to non-conjugated anti-Tac. Applicant further states that page 17 of the instant specification discloses that the ratio of anti-Tac to ^{90}Y -conjugate greatly facilitates the effectiveness of the instant method and that it is an important attribute of the claimed invention.

However, this Waldmann (Imp. Adv. Oncol.) reference authored by applicant appears to teach the use of same 5-15 mCi ^{90}Y -labeled anti-Tac antibody disclosed in Waldmann (Leukemia, 1993, cited as reference 22 in Waldmann, Important Adv. Oncol., 1994 and of record in the instant application, see 892 and the next section)(see page S154, column 1 or Leukemia, 1993) and which appears to be the same recitation of Waldmann (Ann. Oncol., 1994; page 16, column 1 paragraph 2) relied upon above in the previous section. Therefore, the reference disclosure of 5-15 μCi of ^{90}Y -labeled anti-Tac antibody appears to be a mistake and should be 5-15 mCi ^{90}Y -labeled anti-Tac antibody, as the reference clearly indicates by its own citation as well as by applicant himself. The range of 2-100 mg of anti-Tac antibody provided with 5-15 mCi ^{90}Y -labeled anti-Tac antibody recited in the claims is a broad range as well as 25-75% saturation of total IL-2 receptors and surely would have been encompassed by the use of the same 5-15 mCi ^{90}Y -labeled anti-Tac antibody disclosed in the prior art. Applicant has not provided objective evidence to indicate that the prior art teachings do not meet the effective dosages including the saturation of IL-2 receptors encompassed by the claims.

Incorporating similar arguments in response to the other Waldmann prior art references (Ann. Oncol. and Imp. Adv. Oncol.); applicant argues that Waldmann (Leukemia) provides no teaching or suggestion regarding the claimed ratios.

However, this Waldmann (Leukemia) reference authored by applicant appears to teach the use of 5-15 mCi ^{90}Y -labeled anti-Tac antibody for the treatment of HTLV-1-associated Tac-expressing ATL, thereby providing therapeutic effect (see page S154, column 1). The range of 2-100 mg of anti-Tac antibody provided with 5-15 mCi ^{90}Y -labeled anti-Tac antibody recited in the claims is a broad range as well as 25-75% saturation of total IL-2 receptors and surely would have been encompassed by the use of the same 5-15 mCi ^{90}Y -labeled anti-Tac antibody disclosed in the prior art. Applicant has not provided objective evidence to indicate that the prior art teachings do not meet the effective dosages including the saturation of IL-2 receptors encompassed by the claims.

Applicant argues that the three Waldmann review articles fail to provide the skilled artisan with sufficient guidelines as to the specific ratio for anti-Tac to ^{90}Y conjugate necessary to provide an effective dose. However, for the reasons of record and set forth above; the prior art teachings of these Waldmann references clearly indicate that the use of anti-Tac antibody radionuclide (and cytotoxin) conjugates were known and used at the time the invention was made and that these dosages are encompassed by the instant claimed limitations.

Applicant argues that while Waldmann (Blood) teaches treating disease in humans using ^{90}Y conjugate anti-Tac, it does not teach the therapeutically effective amount to be administered to a patient, i.e. the ratio of conjugated to unconjugated anti-Tac claimed in the instant invention.

However, the combination of references including the Waldmann review articles as the primary references do clearly indicate that the use of anti-Tac antibody radionuclide (and cytotoxin) conjugates were known and used at the time the invention was made and that these dosages are encompassed by the instant claimed limitations.

Applicant argues that while Hakimi et al. Teaches administering humanized antibodies to monkeys in order to determine pharmacokinetics, it does provide any teaching or suggestion of a specific antibody-radionuclide ratio missing from the Waldmann articles.

However, the combination of references including the Waldmann review articles as the primary references do clearly indicate that the use of anti-Tac antibody radionuclide (and cytotoxin) conjugates were known and used at the time the invention was made and that these dosages are encompassed by the instant claimed limitations.

Applicant argues that while Kreitman describes modified toxins to anti-Tac and related pharmacokinetics, it does not suggest the treatment of disease in humans using a conjugated anti-Tac in the specific ratio presently claimed.

However, the combination of references including the Waldmann review articles as the primary references do clearly indicate that the use of anti-Tac antibody radionuclide (and cytotoxin) conjugates were known and used at the time the invention was made and that these dosages are encompassed by the instant claimed limitations.

Applicant argues that while Parenteau describes the use of G-CSF, it does not teach or suggest the proper therapeutic amount for treatment of human necessary to provide effective levels of receptor saturation as it addresses the proper anti-Tac to ^{90}Y conjugate ratio for effective treatment.

In contrast to applicant's addressing the Parenteau reference with respect to anti-Tac antibody radionuclide conjugates, this reference provides the motivation and expectation of success in addressing the additional limitation of providing G-CSF to certain patient populations. The effective dosages of anti-Tac antibody radionuclide conjugates were met by the prior art Waldmann references, which all clearly provided teachings of effective therapy in human patients.

Applicant argues that Kozak et al. provides no disclosure of any in vivo use of ^{90}Y -conjugated anti-Tac and teaches a preference for α -emitting radionuclides. In addition, applicant argues that Diamantstein is merely a review article for discussing anti-IL-2 receptor monoclonal antibody therapy but is silent about the use of radionuclides in immunosuppressive therapy. Further, applicant argues that Order describes the possible use of ^{90}Y conjugated antibodies for treatment of cancer, but does not provide the missing teaching of specific anti-Tac to ^{90}Y conjugate ratios to provide an effective dose. Applicant argues that Wessels describes possible dosages of a variety of radionuclides including ^{90}Y , but does not teach which radionuclides would be preferred and does not teach the critical ratio of anti-Tac to ^{90}Y needed to provide an effective dosage.

Again, applicant argues the references individually and not their combination. Diamantstein and Kozak do not teach the use of an α -emitting isotope at the exclusion of a β -emitting isotope. Wessels and Order provide evidence that a β -emitting isotope is an effective radioisotope in eliminating unwanted cells and therefore would have been applicable to the teachings of Diamantstein and Kozak. It is noted that page 5, paragraph 1 of applicant's disclosure makes no distinction between α -emitting isotope such as $^{212}\text{Bismuth}$ with a β -emitting isotope such as $^{90}\text{Yttrium}$. Applicant is reminded that the instant claims are drawn to pharmaceutical compositions and not methods. The combined references of record clearly provide motivation to conjugated anti-Tac antibodies with various conjugates including a β -emitting isotope such as $^{90}\text{Yttrium}$ as a radio-immunotherapeutic reagent for the reasons of record to eliminate unwanted Tac positive cells observed in a number of T-cell mediated disorders in humans.

The range of 2-100 mg of anti-Tac antibody provided with 5-15 mCi ⁹⁰Y-labeled anti-Tac antibody recited in the claims is a broad range as well as 25-75% saturation of total IL-2 receptors and surely would have been encompassed by the use of the same anti-Tac conjugated antibodies disclosed in the prior art. Applicant has not provided objective evidence to indicate that the prior art teachings do not meet the effective dosages including the saturation of IL-2 receptors encompassed by the claims.

Therefore, applicant's arguments are not found persuasive and the rejection is maintained.

6. The following are the outstanding rejections of record.

A) Claims 1-14, 16, 17, 19-25 are rejected under 35 U.S.C. § 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Waldmann (Ann. Oncol., 1994; 1449, #1) for the reasons of record (Paper Nos. 7, 9, 12).

B) Claims 1-14, 16, 17, 19-25 are rejected under 35 U.S.C. § 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Waldmann (Important Adv. Oncol., 1994) for the reasons of record (Paper Nos. 7, 9, 12).

C) Claims 1-14, 16, 17, 19-25 are rejected under 35 U.S.C. § 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Waldmann (Leukemia, 1993) for the reasons of record (Paper Nos. 7, 9, 12).

D) Claims 1-14 and 16-25 are rejected under 35 U.S.C. § 103 as being unpatentable over Waldmann (Ann. Oncol., 1994; 1449, #1) or Waldmann et al. (Important Adv. Oncol., 1994) or Waldmann (Leukemia, 1993) in view of Hakimi (J. Immunol., 1991), Waldmann et al. (Blood, 1993) and Kreitman et al. (Bioconjugate Chem., 1993) for the reasons of record (Paper Nos. 7, 9, 12).

E) Claim 15 is rejected under 35 U.S.C. § 103 as being unpatentable over Waldmann (Ann. Oncol., 1994; 1449, #1) or Waldmann et al. (Important Adv. Oncol., 1994) or Waldmann (Leukemia, 1993) in view of Hakimi (J. Immunol., 1991), Waldmann et al. (Blood, 1993) and Kreitman et al. (Bioconjugate Chem., 1993) as applied to claims 1-14 and 16-25 above and in further view of Parenteau et al. (Transplantation et al.) for the reasons of record (Paper Nos. 7, 9, 12).

F) Claims 25-26 are rejected under 35 U.S.C. § 103 as being unpatentable over Kozak et al. (PNAS, 1986) or Diamantstein et al. (Immunol. Rev., 1986) in view of Order et al. (Int. J. Radiat. Oncol. Biol. Phys., 1986) or Wessels et al. (Med. Phys., 1984) for the reasons of record (Paper Nos. 7, 9, 12).

G) Claims 1-25 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims (1-5, 13, 22 and 28) of copending application Serial No. 07/879,056 in view of Waldmann (Ann. Oncol., 1994; 1449, #1) or Waldmann et al. (Important Adv. Oncol., 1994) or Waldmann (Leukemia, 1993) for the reasons of record (Paper Nos. 7, 9, 12).

Should the claims of copending USSN 07/879,056 be allowed, a terminal disclaimer will be filed at that time. See applicant's amendment, filed 12/6/97 (Paper No. 8),

7. This is a New Grounds of Rejection in view that applicant may intend to incorporate limitations that set forth discrete method steps to monitor soluble IL-2 receptor levels.

Claims 1-14 and 16-25 are rejected under 35 U.S.C. § 103 as being unpatentable over Waldmann (Ann. Oncol., 1994; 1449, #1) or Waldmann et al. (Important Adv. Oncol., 1994) or Waldmann (Leukemia, 1993) in view of Hakimi (J. Immunol., 1991), Waldmann et al. (Blood, 1993) and Kreitman et al. (Bioconjugate Chem., 1993) for the reasons of record (Paper Nos. 7, 9 12) and further in view of art known methods to monitor soluble IL-2 receptors, as evidenced by Rubin et al. (Ann. Intern. Med., 1990).

And claim 15 is rejected under 35 U.S.C. § 103 as being unpatentable over Waldmann (Ann. Oncol., 1994; 1449, #1) or Waldmann et al. (Important Adv. Oncol., 1994) or Waldmann (Leukemia, 1993) in view of Hakimi (J. Immunol., 1991), Waldmann et al. (Blood, 1993), Kreitman et al. (Bioconjugate Chem., 1993) and Rubin et al. (Ann. Intern. Med., 1990) as applied to claims 1-14 and 16-25 above and in further view of Parenteau et al. (Transplantation et al.) for the reasons of record (Paper Nos. 7, 9 12).

The teachings of Waldmann (Ann. Oncol.), Waldmann et al. (Important Adv. Oncol), Waldmann (Leukemia) in view of Hakimi, Waldmann et al. (Blood, 1993) and Kreitman et al. (as well as Parenteau et al.) are of record.

The prior art of record does not disclose generating effective doses that achieve 25-75% saturation of IL-2 receptors per se. However, it was art known and routinely practiced to monitor soluble IL-2 receptors in various disease states at the time the invention was made, as evidence by Rubin et al. (See entire document). Rubin also discloses that such information would be useful in monitoring the efficacy and management of therapeutic treatment.

Also, the Waldmann review articles all disclose the association of IL-2 receptors and various diseases encompassed by the claimed invention as well as it was important to maintain the activity levels of anti-Tac antibody therapies in treating such diseases (see entire documents). The combined references of record also address the importance of pharmacokinetic analyses. Therefore, it would have been obvious to one of ordinary skill in the art to select for appropriate ratios of anti-Tac antibody and conjugate ratios as well as the level of saturation in vivo to achieve therapeutic efficacy in the face of soluble IL-2 receptors in patients. It would have been recognized that there would have been a range of therapeutic doses since differences in the nature of diseases as well as individual patients were known and expected in the art at the time the invention was made. Also, the combined references clearly taught efficacy of anti-Tac antibody conjugate therapies including human patients, therefore, it would have been obvious to establish parameters or calculations associated with antibody-conjugate ratios as well as saturation levels based upon such therapeutic successes and pharmacokinetic studies. Therefore, it would have been obvious to establish via pharmacokinetic studies as well as clinical trials bioavailability information to predict a dose of total anti-Tac antibody conjugates that was sufficient to overcome the effect of soluble IL-2 receptor levels without diminishing antibody specific activity. This would have resulted in the effective dosages encompassed by the claimed limitations, including ratios of anti-Tac to conjugates as well as IL-2 receptor saturation levels

As indicated of record, the references clearly teach the same amount or nearly the same amount of anti-Tac antibody conjugates for the same methods by the same person as that presently claimed. Applicant has not provided sufficient objective evidence to distinguish between the amount of anti-Tac antibody conjugates taught or known by virtue of the combined references differs from that presently claimed. The claimed effective dosages are either taught by the references or it would have obvious to one of ordinary skill in the art at the time the invention was made to provide dosages encompassed by the claimed methods and compositions in meeting the needs of either reducing or eliminating measurable or assessable disease. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to determine and establish the parameters including antibody-conjugate ratios and IL-2 receptor saturation associated with anti-Tac antibody conjugate efficacy in various therapeutic modalities. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention was a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

8. Claims 1-18 and 24-25 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The instant claims are indefinite in their recitations of "said ratio based upon soluble IL-2 receptor levels, such that 25 to 75% saturation of total IL-2 receptors is provided" (recited in claim 1) or "wherein the effective dose is provided in a ratio of anti-Tac to cytotoxin-conjugate, said ratio sufficient to produce 25 to 75% saturation of IL-2 receptors by said cytotoxin conjugate" (recited in claim 24) because it is unclear whether these limitations are properties of effective dosages already claimed or whether these limitations are drawn to discrete and additional method steps.

The amendments must be supported by the specification so as not to add any new matter.

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee can be reached on (703) 308-2731. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1800 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014 or (703) 308-4242.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [lila.feisee@uspto.gov].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Phillip Gambel, Ph.D.
Patent Examiner
Group 1800
November 24, 1997

A handwritten signature in black ink, appearing to read "Phillip Gambel", written in a cursive style.